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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,336	BIRCH ET AL.	
	Examiner	Art Unit	
	Umamaheswari Ramachandran	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16, 19, 38, 39, 41, 48-66, 67-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 19, 38, 39, 41, 48-66, 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 10/17/2007 amending claims 48, 49, 51,61 and adding new claims 67-69. Claims 17-18, 20-37, 40, 42-47 have been canceled. Claims 1-16, 19, 38, 39, 41, 48-66, 67-69 are pending and are being examined on the merits herein.

Response to Remarks

The rejection of claims 48-52 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn due to the amendment of claims. The objection of claim 61 is withdrawn due to the amendment of claim 61. The rejection of claims 51 and 52 under U.S.C 112 (2) is withdrawn due to the amendment of claims 51 and 52. The rejection of claims 7, 11, 38, 39, 41, 48-55, 57-62, and 64-66 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-34, 38-50, and 56-59 of copending Application No. 10/508,315 is withdrawn due to the abandonment of the copending Application No. 10/508,315 on 6/25/2007. Claims 1-15, 38-39, and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805), in view of Watts et al. (Applicant-cited reference on IDS: WO 98/47535), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" Remington: The Science and Practice or Pharmacv, Nineteenth Edition, Volume 1. Easton, PA: Mack, **1995**. pp. 613-615), and Nairn (Nairn, J. G. Solutions, Emulsions, Suspensions and Extracts" Remington: The Science and Practice or Pharmacv, Nineteenth Edition, Volume 2. Easton, PA: Mack,

1995. p. 1502). The rejection is maintained. Applicant's arguments are addressed below. Claims 16 and 53-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1). The rejection is maintained. Applicant's arguments are addressed below. Claims 19 and 60-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195 A2, January 3, 2002). The rejection is maintained. Applicant's arguments are addressed below. Claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917. The rejection is maintained. Applicant's arguments are addressed below. Applicants' amendments necessitated the modified rejections presented in this office action. Thus the office action is made Final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 38-39, 41, 48-52, 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.), in view of Watts et al. (Applicant-cited reference on IDS: WO 98/47535, October 29, 1998), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 1. Easton, PA: Mack, **1995**. pp. 613-615.), and Nairn (Nairn, J. G. Solutions, Emulsions, Suspensions and Extracts" Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 2. Easton, PA: Mack, **1995**. p. 1502.).

Eriksen et al. teach an aqueous solution suitable for intranasal administration which comprises 2 mg/ml of buprenorphine as the salt buprenorphine hydrochloride. The composition of Eriksen et al. further comprises dextrose (see "The spray-device and the buprenorphine-spray solution" and "Procedure" on pp. 803-4). Due to the fact that Eriksen et al. do not add divalent metal cations into the composition during the preparation, it can be inferred that Eriksen et al. teach the composition as being

substantially free of divalent metal cations. Eriksen et al. also teach a method for the preparation of said composition ("The spray-device and the buprenorphine-spray solution" on p. 803). Eriksen et al. teach a nasal delivery device loaded with said solution, wherein the nasal delivery device is a spray device ("The spray-device and the buprenorphine-spray solution" on p. 803). Eriksen teach that buprenorphine is a μ-partial agonist opioid analgesic recommended for the treatment of moderate to severe pain (p 803, col. 1, lines 1-2) and teach administration of buprenorphine intranasally to volunteers. The reference teach mean plasma concentration of buprenorphine ranging from 0.16 ng/ml to 1.65 ng/ml and produces a plasma concentration of 1.49 ng/ml in 20 minutes (Table 3). The reference teach a plasma concentration of 0.62 ± 0.06 ng/ml around 120 min after administration of buprenorphine (Table 3).

Eriksen et al. do not teach that the solutions comprise pectin, wherein the pectin is at a concentration of 5-40 mg/ml, 10-30 mg/ml, or 10-40 mg/ml, and wherein the pectin has a degree of esterification of less than 50%, or a degree of esterification of from 10-35%. Eriksen et al. also do not teach the solution as having a pH of from 3-4.2 or from 3.5-4. Eriksen et al. do not teach the osmolality of the solution as being from 0.35 to 0.5 osmol/kg.

Watts et al. teach solutions that are substantially free of divalent metal ions and which comprise therapeutic agents and pectin with a low degree of esterification for administration intranasally, and specifically wherein the degree of esterification of pectin is less than 50%, and more preferably less than 35%. The pectin is present at a concentration of from 1 to 100 mg/ml (p. 2, lines 23-26; p. 9, lines 22-27; p. 11, line 21 -

p. 12, line 5; p. 12, lines 22-27; Example 1; claims 1-2). Watts et al. also teach that said solution has a pH from "2 to 9, more preferably from 3 to 8 and most preferably from 4-7." (p. 16, line 29 -p. 17, line 3). Watts et al. teach that "the lower the DE of the pectin, the lower the pH at which the composition will gel. pH may be adjusted in accordance with techniques which will be well known to those skilled in the art" (p. 17, lines 3-6). Thus, Watts et al. suggest optimizing the pH of the composition within the disclosed preferred ranges using routine experimentation based on the pectin that is incorporated into the composition. Watts et al. also teach that the solutions comprising pectins and therapeutic agents should have a concentration of pectin greater than 4 mg/ml for solid gel formation upon intranasal administration (Example 1).

Nairn teaches that nasal solutions are usually isotonic (p. 1502).

Reich et al. teach, "The term isotonic, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic." (p. 613). Reich et al. also teach, "Serum osmolality often is stated loosely to be about 300 mOsmol/L." (p. 615).

Although the osmolality of the intranasal solution in the instant claim 11 is slightly higher than serum osmolality, this is necessitated by the amount of pectin that is required by the teachings of Watts et al. in order that the solution gels upon intranasal administration (Example 1). Therefore, the osmolality of a solution for intranasal administration that comprises low DE pectin as the gelling agent should be close to isoosmotic and should have the required concentration of pectin to achieve gelling upon administration as taught by Narin, Reich et al., and Watts et al.

It would have been obvious to a person of ordinary skill in the art at the time of invention to incorporate pectins having a low degree of esterification into the solutions of Eriksen et al., to adjust the pH and osmolality of said solution to the appropriate ranges taught by Watts et al., to incorporate the solution into a spray device, and to intranasally deliver the solution in a method of inducing analgesia.

The person of ordinary skill in the art would have been motivated to introduce the gelling capacity taught by Watts et al. into the solutions of Eriksen et al. because this would improve the duration of the desired plasma concentration of the active agent delivered from the compositions in the method taught by Eriksen et al. through enhanced retention of the agent in the nasal cavity. As Watts et al. teach, "It would be most beneficial, due to ease of use and of administration, to have available a simple solution spray system that was suitable for the administration of drugs to the nose and, better still, for the drugs administered via such a system to have a long retention in the nasal cavity," (p. 2, lines 23-26). The person of ordinary skill in the art would have expected success because the mucoadhesives are designed for effecting retention of active agents in nasal spray solutions in the nasal cavity upon administration.

Eriksen teach a plasma concentration of 0.62 ± 0.06 ng/ml around 120 min after administration of buprenorphine (Table 3). The reference does not teach maintaining the plasma concentration of buprenorphine to 0.8-2.0 ng/ml for at least 2 h.

It would have been obvious to one of ordinary skill in the art to formulate the composition comprising buprenorphine administering intranasally to produce a plasma concentration of buprenorphine to 0.8-2.0 ng/ml for at least 2 h. Eriksen teach a plasma

concentration of 0.62 ± 0.06 ng/ml around 120 min after administration of buprenorphine The reference's pharmacokinetic characteristics Cmax and Tmax slightly differ from those claimed herein. However, the determination of optimal or workable pharmacokinetic characteristics by routine experimentation is obvious absent showing of criticality of the claimed characteristics. It would have been obvious to one of ordinary skill in the art to routinely adjust the concentrations of the drug or the concentrations of the solvents or carriers to obtain the desired pharmacokinetic parameters.

Claims 16 and 53-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1).

Eriksen et al. teach the composition comprising dextrose and buprenorphine hydrochloride, as discussed above. The concentration of buprenorphine in the composition is 2 mg/ml, which is within the instantly claimed ranges. Eriksen et al. teach preparation of the composition and incorporation of said composition into a spray device for intranasal delivery ("The spray-device and the buprenorphine-spray solution" on p. 803). Eriksen et al. also teach a method of inducing analgesia comprising administering said composition intranasally ("Procedure" section on pp. 803-4).

Eriksen et al. do not teach the solutions as further comprising chitosan or hydroxypropylmethyl cellulose (HPMC), or as having a pH from 3 to 4.8.

Koochaki teaches a composition comprising a drug and a pharmaceutical carrier, wherein the carrier comprises a non-ionic cellulose ether, preferably HPMC, and a

chitin-derived polymer, which may be chitosan (p. 2, lines 38-44; Example 1; Example 2; claims 1-3 and 6). Koochaki teaches that the compositions are "for application to the mucosa of the nasal cavity." (claim 1). Koochaki teaches a method of incorporating the HPMC and chitosan into a composition containing a drug and adjusting the pH to about 4.5 (Example 1).

It would have been obvious to a person of ordinary skill in the art at the time of invention to modify the procedure for preparing the buprenophine nasal spray composition of Eriksen et al. in order to incorporate chitosan and HPMC as taught by Koochaki, to modify the pH as taught by Koochaki, to incorporate the composition into a spray device, and to administer the composition in a method of inducing analgesia to arrive at the instantly-claimed invention.

The person of ordinary skill in the art would have been motivated to incorporate the mucoadhesives of Koochaki into the solution of Eriksen et al. because, as taught be Watts et al., this would improve retention of the drug in the nasal cavity after administration, thus improving the duration of the desired plasma concentration of the active agent (see above). The person of ordinary skill in the art would not even need to look to Watts et al. for motivation because it is very well known in the art that increasing the retention of an active compound in the nasal cavity that is administered intranasally will improve the time that the compound is available to be absorbed in the body. The person of ordinary skill in the art would have expected success absent evidence to the contrary because chitosan and HPMC are routinely used pharmaceutical excipients that would be expected to be compatible with buprenorphine.

Claims 19 and 60-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195 A2, January 3, 2002).

Eriksen et al. teach the composition comprising dextrose and 2 mg/ml buprenorphine as buprenorphine hydrochloride, as well a method of preparing said composition, a nasal spray device for intranasal administration of said composition, and a method of inducing analgesia comprising intranasally administering said composition, as discussed above.

Eriksen et al. do not teach the compositions as further comprising chitosan and polyoxyethylene-polyoxypropylene copolymers, or the pH of the solution as being from 3 to 4.8.

Williams et al. teach, "A composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof." (claim 1; Examples 1 and 2). Williams et al. further teach, "the mucoadhesive is a block polymer of ethylene oxide and propylene oxide." (Claim 6 and p. 7, line 10 –p. 8, line 11). Williams et al. teach, "Preferably, the pH of the composition is within the range of from about 2 to about 9, more preferably, about 3 to about 7, even more preferably about 4 to about 5, and optimally about 4.5." (p. 10, lines 26-30).

It would have been obvious to a person of ordinary skill in the art at the time of invention to modify the procedure for preparing the buprenophine nasal spray

composition of Eriksen et al. to incorporate the mucoadhesives of Williams et al. into the solution taught by Eriksen et al., to modify the pH as taught by Williams et al., to incorporate the composition into a spray device, and to administer the composition in a method of inducing analgesia, to arrive at the instantly-claimed invention.

The person of ordinary skill in the art would have been motivated to incorporate the mucoadhesives of Williams et al. into the solution of Eriksen et al. because, as taught be Watts et al., this would improve retention of the drug in the nasal cavity after administration, thus improving the duration of the desired plasma concentration of the active agent by increasing retention of the agent in the nasal cavity (see above). As discussed above, the person of ordinary skill in the art would not need Watts et al. because the utility and purpose of nasal spray solutions for delivering pharmaceuticals is well-recognized in the art. The person of ordinary skill would have further been motivated with a reasonable expectation of success because Williams et al. teach that buprenorphine is a suitable opioid for incorporation into compositions containing the specified mucoadhesives for intranasal delivery (p. 4, lines 11-26).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants of the same invention.

'917 teaches a composition adapted for intranasal delivery comprising a methane sulphonate salt of an opioid analgesic, and further comprising chitosan or a salt or derivative thereof (claims 1 and 2). '917 also teaches a method of treating pain comprising administering to the nose a methane sulphonate of an opioid analgesic (claim 8), and a nasal drug delivery device containing as a drug a methane sulphonate salt of an opioid analgesic (claim 12).

'917 does not teach use of buprenorphine in the compositions or methods as the opioid analgesic.

It would have been obvious to a person of ordinary skill in the art at the time of invention to generate a methane sulphonate salt of buprenorphine, put it into the composition suitable for intranasal delivery taught in '917, place the composition into the

nasal delivery device taught in '917, and use the composition in the method of treating pain taught in '917, to make the inventions the current application.

The person of ordinary skill in the art would have been motivated to use buprenorphine in the compositions and methods of '917 because '917 teaches compositions for intranasal administration which comprise analgesics generally, and buprenorphine is a well known analgesic that is administered intranasally. The person of ordinary skill in the art would have been further motivated because '917 states, this would "provide an increased absorption of the drug." (column 2, lines 66-67). The person of ordinary skill would have expected success absent evidence to the contrary.

Response to Arguments

Regarding the rejection of claims 1-15, 38, 39, and 41 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Watts et al. (WO 98/47535), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" in Remington: The Science and Practice or Pharmacv, Nineteenth Edition, Volume 1. (1995) Easton, PA: Mack. pp. 613-615), and Nairn (Nairn, J. G. "Solutions, Emulsions, Suspensions and Extracts" in Remington: The Science and Practice or Pharmacv, Nineteenth Edition, Volume 2. (1995) Easton, PA: Mack. pp. 1495, 1496 and 1502), Applicants' argue that the present invention is concerned with the provision of bupernorphine composition which provide relatively high plasma concentration, at a relatively short time after administration and relatively well sustained. It is noted that these are not limitations in the claims. Further,

even if these were limitations in the claims, they are inherent properties of the formulations suggested by Eriksen et al. in view of Watts et al.

Applicant argues that Watts et al. teach away from a formulation with the desired properties of a rapid onset of analgesia, a closer to optimum level of analgesia, or analgesia that is well sustained because Watts et al. teach that if the formulation is for local administration, the formulation should not enhance transmucosal absorption, and if for systemic administration, the formulation should not give rise to any significant plasma concentration. Firstly, it is noted that these are not limitations in the claims. Secondly, it is pointed out that on p. 3, ll. 16-25, Watts et al. teach that incorporation of the pectins into nasal spray solutions produces a simple nasal delivery system that can be used to modify (increase or decrease) the absorption characteristics when administering drugs systemically or locally. Watts et al. teach that when the drugs are to be administered locally, the system should not enhance absorption to effect increased systemic delivery. However, this is only one of the options for modulating the absorption characteristics, and it is particularly only relevant to local delivery of the drugs. Because buprenorphine is for systemic delivery, it would have been obvious to a person of ordinary skill in the art that the pectin gelling agents could be used to increase systemic delivery of the active compounds, if desired. Also, at the Applicant-cited passage p. 14, l. 12 on, Watts et al. teach that the nasal spray composition can be formulated to alter (increase or decrease) the rate of transport in the general circulation, not only decrease as Applicant asserts. See also p. 14, lines 20-24, where Watts et al. teach that the "invention may thus be used for the modification of the systemic

absorption of mucosally administered drugs." Further, on p. 14, Watts et al. suggest that the formulation can be used to deliver apomorphine and fentanyl, which are systemic analgesics similar to buprenorphine. Thus, Watts et al. do not teach away from systemic administration of buprenorphine with their mucoadhesives.

Regarding the rejection of claims 16 and 53-59 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1), Applicant argues that the composition of Eriksen et al. differs from the present formulations in that it does not contain chitosan and hydroxypropylmethylcellulose (HPMC). Regarding the presence of chitosan and HPMC, it is acknowledged that Eriksen et al. do not teach these additives in the formulations. This is why the Koochaki reference was applied. Koochaki teaches the addition of the mucoadhesives chitosan and HPMC to retain the active agent in the nasal cavity for sustained delivery. Although Koochaki does teach that the formulations are in a powder form, it would have been obvious to the person of ordinary skill in the art that the mucoadhesives chitosan and HPMC could also be used in a solution that gels upon introduction into the nasal cavity to achieve sustained delivery by simply lowering the concentration of the mucoadhesives. Koochaki in fact teaches that this is a known strategy in the pharmaceutical formulation art (p. 2, lines 16-22). Koochaki does not teach that this strategy is ineffective. He merely teaches that the powder formulation is an alternative to the solution formulation that gels on the mucosa. The optimal concentration of the mucoadhesives that would allow sprayability and mucoadhesion could be arrived at

through routine experimentation by the ordinary skilled artisan. Thus, it would have been obvious that the mucoadhesives they teach, chitosan and HPMC, could be used in nasal spray solutions that gel on the mucosa to achieve sustained release of the active agent.

Applicants' argue that the levels of chitosan and HPMC in the present formulation are in the range of 0.2 to 35 mg/ml and Koochaki's formulation contain percentages by weight that are higher than the claimed invention. In response, the reference teach 90-10% by weight of non ionic cellulose ether derivative and 10-90% of chitin derived polymer. For example, if the amount of cellulose ether derivative is 10% and the chitin polymer derivative is 10% it adds up to 20% or 20 g /100 mg or 100 ml of the solution. The amount of an ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention. Koochaki clearly teaches the safety and benefits of chitosan and HPMC carrier for nasal administration. Hence it would have been obvious to one of ordinary skill in the art to routinely optimize the ingredients to achieve the desired composition.

Regarding the rejection of claims 19 and 60-66 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**,

41, 803-805) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195), Applicant argues that the ordinary skilled artisan would not consider Williams for the provision of a formulation to provide a relatively high plasma concentration because Williams et al. is directed to local delivery of analgesics, whereas the instantly claimed formulations are for systemic delivery of the analgesic. It is noted that the intended use of the composition does not lend patentability to the composition. Williams et al. exemplify buprenorphine as a suitable opioid for formulation with the polyoxyethylene-polyoxypropylene copolymer mucoadhesives (p. 4, lines 11-13). Regardless of whether the formulation is for systemic or local administration of the buprenophine, the compositions are identical. Eriksen et al. teach that introduction of buprenorphine into the nasal cavity achieves systemic delivery of the active agent for inducing analgesia. Thus, the person of ordinary skill in the art would understand that using the excipients of Williams et al. in a nasal spray solution containing buprenorphine would achieve sustained systemic delivery of the agent through the nasal mucosa, as opposed to sustained local delivery through the buccal mucosa. Finally, Williams et al. teach that chitosan can also be incorporated with the polyoxyethylene-polyoxypropylene copolymer mucoadhesives (p. 7, ll. 10-11). Applicants' argue that there is no direction within Williams that lead to the combination of chitosan and polyox and no indication that it can lead to formulations to provide high maximum plasma concentration, relatively short time after administration and relatively well sustained. Williams clearly teach mucoadhesives such as chitosan, pectin, HPMC, and block copolymers of polyoxy propylene and polyoxy ethylene (as preferred) for adherence to the mucous

membrane for a period of time sufficient to locally deliver a therapeutically effective amount of a composition of the invention. It would have been obvious to one of ordinary skill in the art to combine mucoadhesives and formulate with buprenorphine to improve the duration of the desired plasma concentration of the active agent by increasing retention of the agent in the nasal cavity. As stated above, the relatively high maximum plasma concentrations that are rapidly achieved and well sustained are not limitations in the claims. Further, even if these were limitations in the claims, they are inherent properties of the formulations suggested by Eriksen et al. in view of Williams et al.

Regarding the rejection of claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 on the ground of nonstatutory obviousness-type double patenting over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917, Applicant argues that there is no teaching of "formulations for the nasal cavity that comprise buprenorphine or a salt thereof". As pointed out in the previous Office Action, '917 teaches a composition adapted for nasal delivery comprising a methane sulphonate salt of an opioid analgesic (claims 1). At col. 3, ll. 21-25, buprenorphine is exemplified as an opioid analgesic for incorporation into the nasal delivery formulation. Thus, '917 teaches "formulations for the nasal cavity that comprise buprenorphine or a salt thereof", and the double-patenting rejection is properly maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the modified rejections presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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